Detecting multiple sclerosis cortical lesions post-mortem using 7 Tesla Magnetic Resonance Imaging

B. Yao[1], S. Hametner[2], P. van Gelderen[1], H. Merkle[1], F. Cantor[3], H. McFarland[3], H. Lassmann[2], J. H. Duyn[1], and F. Bagnato[3]

[1]AMRI, NINDS, National Institutes of Health, Bethesda, MD, United States, [2]Centre for Brain Research, Medical University, Vienna, Austria, [3]NIB, NINDS, National Institutes of Health, Bethesda, MD, United States

Introduction: Although originally considered a white matter (WM) disease, it is now clear that focal cortical grey matter (GM) pathology is an important component of multiple sclerosis (MS). Presently available magnetic resonance imaging (MRI) techniques fail in detecting the actual amount of cortical lesions (CLs). The reason for such a failure is twofold: (i) the small size of CLs relative to image resolution and (ii) the low contrast between CLs and the surrounding healthy or seemingly normal GM tissue. MRI at ultra-high field strengths such as 7 Tesla (T) has the potential to superbly enhance MS-induced CLs visibility. First, ultra-high filed MRI yields images at highest resolution. Second, a greatly enhanced T_2^* contrast is offered by scanning at 7 T. Moreover, the R_2^* ($1/T_2^*$) maps are sensitive to the local susceptibility shifts induced by different tissue contents, such as iron and myelin lipid [1,2]. Fueled by this motivation we here apply ultra-high resolution R_2^* maps to detect and evaluate CLs and their subtypes *post-mortem*.

Methods: Nine formalin-fixed brain 1-cm thick coronal slices of brains from two donors who died of MS (55 y/o female with primary progressive MS and 70 y/o male with secondary progressive MS) were scanned. We used a 3D T_2^*-weighted multi-echo gradient echo ME-GRE sequence. The tissue slices were scanned on a GE 7T scanner with 0.2 mm isotropic resolution and TE = 8.7, 25.2, 41.7, 58.2 ms, TR = 180 ms, flip angle = 10º, bandwidth = ±31.25 kHz. Quantitative R_2^* maps were obtained by using mono-exponential fitting. Three experienced investigators detected the presence of CLs in MRI and classified those into: Type I: adjacent even invading WM to some extent; Type II: intracortical transversing the cortex for several layers or entirely but without invading the WM and Type III: subpial. Control regions of interest (ROIs) were carefully selected from the normal appearing grey matter (NAGM) in similar anatomical locations. R_2^* of CLs and corresponding NAGM-ROIs were measured. An ANOVA test was used to investigate differences in relative changes in R_2^* between CLs and corresponding NAGM ROIs. Immunocytochemistry for proteolipid protein (PLP) was performed to identify cortical demylination [3].

Results: We counted 102 CLs. 28 CLs were seen in the 3 slices of the PPMS brain. 74 were identified in the 6 slices of the SPMS case. R_2^* values of 21 CLs with 7 in each type were paired-compared with 21 control NAGM regions. A mean difference of -7.6 Hz was found in R_2^* of CLs with respect to NAGMs (Fig. 1). No significant difference in the relative changes in R_2^* between CLs and their corresponding NAGM ROIs among the three types of CL was found by ANOVA. PLP staining confirmed the presence of CLs identified by MRI. We show an example in Fig. 2 where one can see in brown– intact myelin; green –focal full demyelinated plaques in WM; light blue – partial WM demyelination; red – full cortical demyelination; yellow – partial cortical demyelination.

Discussion: High resolution R_2^* map obtained in 7 T shows a strong sensitivity in detecting myelin-induced susceptibility shifts, thus provides us a new tool in detecting CLs in MS. Further quantitative analysis aiming at investigating the correlations between R_2^* changes and degree of demyelination and/or neuronal loss in the cortex is necessary and currently being performed. Each CL type is potentially informative, regarding mechanisms of demyelination and features of the immune response, or demyelinating inflammatory environment. For example, Type I CL could be a demyelination extended from WM, while Type III may be associated with a factor(s) that diffused from the brain pial surface.

References: [1] Yao B et al, *Proc. ISMRM* 2009: 342; [2] Fukunaga M et al, *Proc. ISMRM* 2009: 47; [3] Kutzelnigg A et al, *Brain* 128:2705-12, 2005
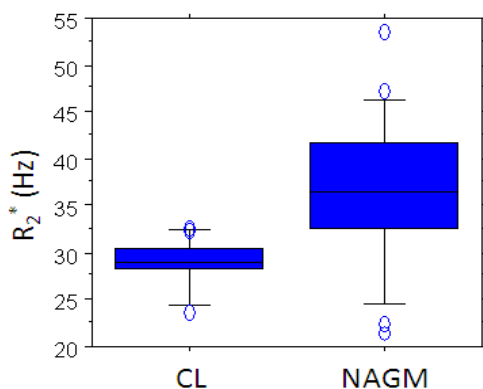
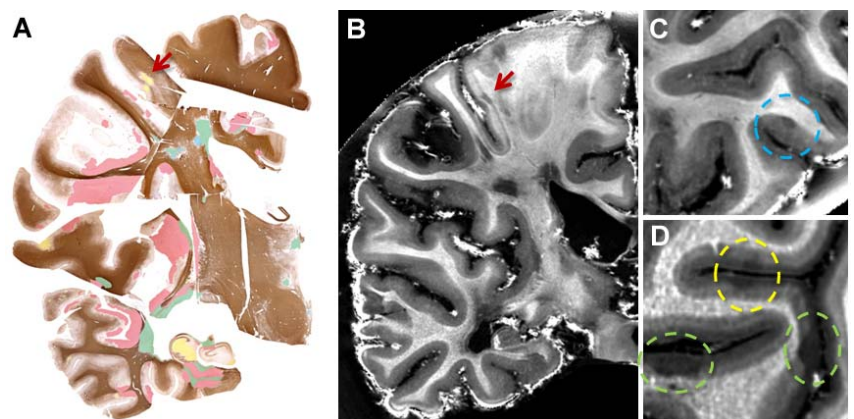**Fig. 1**: Comparison of R_2^* values between CLs and control Normal Appearing Grey Matters.

Fig. 2: A Neuropathology staining; **B** corresponding R_2^* map. Same CLs can be detected clearly in the R_2^* maps (e.g., red arrows); **C** and **D** R_2^* map of representative Type I (blue), II (green) and III (yellow) lesions.